Periodical

AMERICAN JOURNAL OF PHARMACY

and

THE SCIENCES SUPPORTING PUBLIC HEALTH

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CHARLES E. CASPARI
1875—1942
(see "Our Cover", p. 278)

AUGUST
1943

The College .....

and its EDUCATIONAL POLICY

The Philadelphia College of Pharmacy and Science was the pioneer in pharmaceutical education in America. It has constantly moved forward with the times during its century and a quarter of existence, and along with other recognized colleges of pharmacy in this country it has developed its training to such a point that the broad course leading to the degree of Bachelor of Science in Pharmacy is equivalent in dignity, in results, and in prestige, to the Bachelor of Science course in kindred academic fields.

Now, this Institution consists of four schools, namely, the schools of Pharmacy, of Chemistry, of Biology and of Bacteriology. These four schools are on the same academic level in curricula and degrees and shall continue on the present academic program adopted early in 1942. This is a course completable in a little less than three years, made possible through the elimination of vacation periods—a course in which there has been no sacrifice either in quantity or quality of instruction.

To integrate into the current wartime plan of acceleration, the 1943 entering class commenced studies late in June. Students in that group will qualify for promotion to the sophomore class in March, 1944. Therefore, so that there be no diversion of teaching attention from those who are now freshmen, there will be no other entering class until March 15, 1944. At that time properly qualified students will commence their studies here in all four schools. They may qualify for their degrees by December, 1946, providing that the war continues to demand the present acceleration.

Interested persons who had planned to enter college in September of this year should not feel that this delay necessitates a loss of time. It should be remembered that those who come to college with some practical experience usually are better students, and there is, at the present, quite a demand for apprentice help in professional endeavors, and, also, in the war industries. Such a period of work will, in addition, allow the student who is to start his studies early next year to build a financial reserve that will stand him or her in good stead during the period of education, for there will be no summer vacations in which to work and earn additional funds.

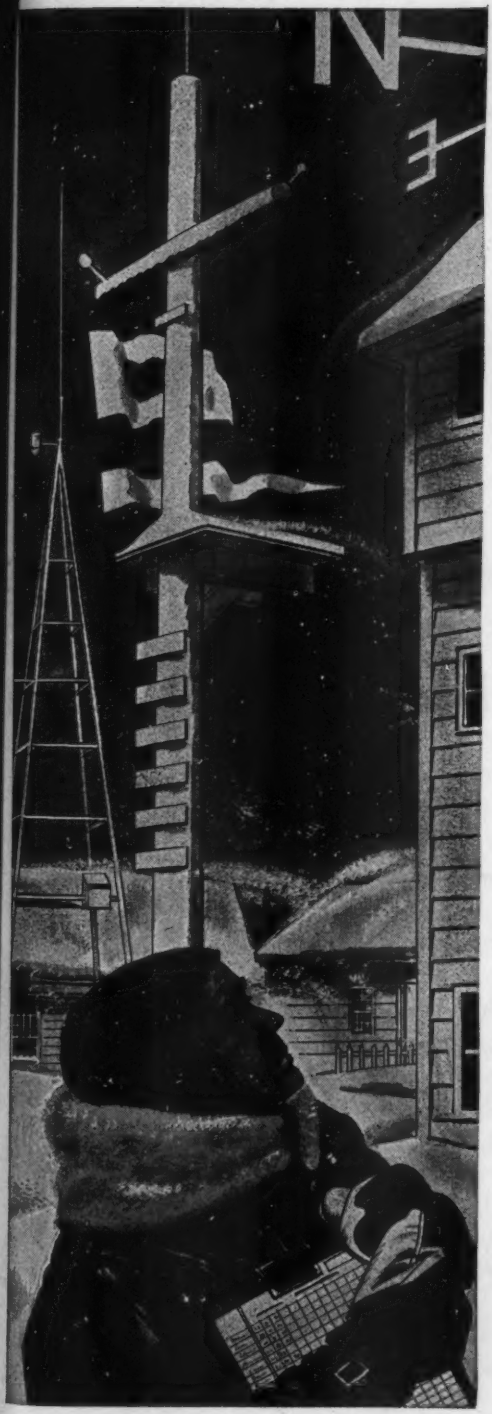
The Registrar will be pleased to supply details of the entrance requirements and other data pertinent to those who would be interested in entering this College on March 15, 1944, or in the following class, which will start on October 30, 1944.

PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

43rd Street, Kingsessing and Woodland Avenues

PHILADELPHIA 4, PENNSYLVANIA

WATCHMAN, WHAT OF THE WINTER?



• In temperate zones, laymen and meteorologists alike know that winter brings foul weather and a tremendous increase in colds and similar disorders of the upper respiratory tract.

Moreover, if last year's record[1] may be regarded as characteristic, the weekly incidence of colds this winter will rise from a July minimum of about 6,500,000 to around 21,000,000 in mid-February.

As the number of colds increases, working efficiency declines. It has been estimated that one-half of all work-time lost in war industries as a result of illness is lost because of the common cold. Thus, during a single four-week period in midwinter, colds accounted for the loss of approximately 1,600,000 man-days of work in war industries alone.

Fortunately, the incidence and severity of colds may be considerably reduced by oral administration of antigens derived from bacteria believed responsible for the severity of the symptoms and duration of the disease. *'Vacagen' Oral Cold Vaccine Tablets* are exceptionally effective. Each provides the water-soluble, antigenic derivatives of approximately 60,000 million organisms of ten different types associated with infections of the upper respiratory tract:

Pneumococcus* (*Diplococcus pneumoniae*)	25,000 million
Streptococcus**	15,000 million
Influenza bacillus (*Hemophilus influenzae*)	5,000 million
M. catarrhalis (*Neisseria catarrhalis*)	5,000 million
Friedlander bacillus (*Klebsiella pneumoniae*)	5,000 million
Staphylococcus (*aureus*)	5,000 million

*Types 1, 2 and 3
**Hemolytic, non-hemolytic and viridans

The fresh antigens, extracted from *living* bacteria, are rapidly frozen, dehydrated under high vacuum, and made into *enteric-coated* tablets for oral administration.

'Vacagen' Oral Cold Vaccine Tablets are supplied in bottles of 20, 100, 500 and 1,000. Sharp & Dohme, Philadelphia, Pa.

'VACAGEN'

ORAL COLD VACCINE

1. Gallup, G.; American Institute of Public Opinion Survey, February, 1943.

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Eli Lilly and Company is especially proud of its veterans, among whom is James A. Stone, of Lincoln, Nebraska. Mr. Stone joined the Lilly organization in 1913, only to leave a few years later to engage in the retail drug business. He returned to his post in 1923 and is now in his twenty-first consecutive year. For the last several years his son, James Jr., has represented the house in parts of Minnesota and North Dakota.

BUY WAR BONDS AND STAMPS

AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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OUR COVER

CHARLES E. CASPARI

CHARLES E. CASPARI was the son of an illustrious father, in whose footsteps he followed with distinction. The elder Caspari was one of those stalwarts of early American pharmacy who laid the groundwork for the tremendous progress made in pharmacy in more recent times.

As a boy Charles was effectively impressed with science, and at the early age of seventeen he began his studies at Johns Hopkins University, where he obtained in 1900 his Ph. D. degree in Chemistry. He then accepted a teaching post at Columbia, which he left to join the research staff of the Mallinckrodt Chemical Works. Some time later he joined the faculty of the St. Louis College of Pharmacy, which became his lifelong interest thereafter.

Dr. Caspari's works and efforts in pharmacy and pharmaceutical education are well known, and the growth and advance of the St. Louis College of Pharmacy is a monument to his labor. It is only proper that this institution should now seek to perpetuate his name as well as continue his efforts by the creation of the Caspari Endowment Fund as a memorial to this man whose energies contributed so much during his life. To this end we lend our moral support, and this issue is therefore dedicated to that educator with whose name the St. Louis College of Pharmacy was so long identified.

EDITORIAL

AN OBLIGATION NOT A GRATUITY

ELSEWHERE in this issue there is a page devoted to both a memorial of a pharmaceutical educator and an endorsement of the current effort by the college in which he taught to raise a memorial endowment fund bearing his name. We are happy to do what little we can to promote this worthy cause, but the problem of the financial support of pharmaceutical education transcends any individual school's effort to ease its financial burden.

There are many influences at work today which are molding the pattern of education for the future. One fact, however, is definitely acknowledged by all, namely, that the difference between the cost of administering higher education and that amount paid by the student will increase more and more. State institutions cover this difference with funds raised by taxation, and we have no argument against this plan. It is only proper that the benefits derived by society from education should merit its financial support through taxation. This is well established by our public school system. Private schools are today more than ever in a precarious position due to lowered enrollments which do not proportionately reduce operating costs.

If only state institutions survive we frankly question how long education will remain untrammeled by political dictation. At present, even though state institutions are a major force in education, there remain a number of stout institutions completely free and independent of any state funds or political restraint. It is our opinion that in these schools lie the bulwark of academic freedom. There are, on the other hand, those educators who argue strongly that only state universities represent proper places to impart knowledge and wisdom and that "private institutions" are outmoded organizations carried over from the nineteenth century. Such men, however, overlook the inescapable fact that these private institutions protect even *their* cherished academic freedom, since without them who could predict the regimentation and dictation that would be implemented without fear of effective opposition and action.

We have already seen evidence of the operation of a completely state dominated educational system. Does anyone doubt that in Nazi Germany today there are hundreds of educators who despise the Nazi yoke of tyranny? But how can they speak? All free institutions of learning have been destroyed.

This argument may be answered by those who will cite the basic differences between American and German ideology, explaining that this could not happen here even if the state were in full and complete control. On this premise lies the greatest danger to freedom that we as Americans have ever faced. It can happen here in the field of education as in all else; only by clear thinking and resolute action can it be avoided. By its very nature all government tends to become autocratic unless restraint is imposed upon it.

If that brand of pharmaceutical education is to survive which will continue to give to pharmacy freedom, opportunity and reward for achievement, then those who have greatly benefited from this system must continue, now more than ever before, to support and guarantee the present and future of its free institutions.

The benefits of such support are not just those derived by the colleges and schools receiving such aid, but indirectly all schools benefit as will pharmacy, society and the world. To those in a position to help pharmaceutical institutions of learning through these difficult days we direct this message.

L. F. Tice.

SOLUTION OF MAGNESIUM CITRATE

By P. Robert Rasanen and Joseph B. Burt

The following two articles are the first of a series of studies conducted by Dr. Burt, as a member of the U. S. P. Sub-Committee on Waters, Solutions, Spirits, Syrups and Elixirs. Although carried out prior to the release of the U. S. P. XII, the observations and results reported are of real interest to those who manufacture or use these preparations.—Ed.

THIS solution, which is popular under the name of purgative lemonade, and sometimes erroneously spoken of as citrate of magnesia by laymen, has been a subject for study and comment since it was first introduced into the U. S. P. in 1850. The solution is widely used as a cathartic and in the present day is largely manufactured in commercial pharmaceutical laboratories where the process of filtration, bottling, carbonization, and sterilization is wholly automatic. However, some pharmacists still manufacture it in small quantities when needed. Changes in the formula have been made from time to time as they were found necessary, but each modification has in turn been further criticised. According to Langenhan (1), the problem of stability has been a vital one. Other questions which have been brought up for discussion by Pharmacopœial Committees of Revision have been palatability, the composition of the salt formed in the solution, and which salt is the most desirable from the viewpoint of therapeutic action. More recently a request was submitted by Cook (2) to Sub-Committee No. 12 as to the feasibility of permitting the use of saccharin as an alternative for sucrose so that this solution could be made available to diabetic patients. Another comment was made by Scoville (3) suggesting that the strength of the solution be reduced to four-sevenths of the present requirements, because the official dose of this preparation is 200 cc. and the formula still requires that it be bottled in 350 cc. quantities; consequently after one dose has been administered, 150 cc. of the solution remains. Since this solution will not keep for any length of time once it is opened, this surplus must be discarded. Scoville maintains that weaker solutions will be more palatable, and at the same time dilution of the preparation will contribute to its stability.

History

As stated previously, this preparation was first introduced into the U. S. P. in 1850. The formula (4) included carbonate of magnesia, but was changed to magnesia in 1860 because the carbonate often contained gritty impurities. Four-fifths of the carbonate were dissolved in the citric acid solution and this filtered into the syrup of citric acid, then the remaining fifth of the carbonate was added. The addition of the reserve carbonate was intended to impregnate the solution with carbonic acid by its reaction with the excess citric acid. To effect solution of this reserve carbonate took at least one-half hour and later a precipitate settled out making the solution unfit for medicinal use. This salt was found to be the normal magnesium citrate containing fourteen molecules of water (4). The following table shows the various changes in the formula of this preparation from 1860 up to and including the U. S. P. VIII.

	U. S. P. 1860	U. S. P. 1870	U. S. P. 1880	U. S. P. 1890	U. S. P. VIII
Magnesia	120 gr.				
Magnesium Carbonate		200 gr.	13 Gm.	15 Gm.	15 Gm.
Citric Acid	450 gr.	400 gr.	26 Gm.	30 Gm.	33 Gm.
Syrup of Citric Acid	2 f℥	2 f℥	80 Gm.	120 Gm.	60 cc.
Potassium Bicarbonate	40 gr.	40 gr.	2 Gm.	2.5 Gm.	2.5 Gm.
Distilled Water					
To make	12 f℥	12 f℥	360 cc.	360 cc.	360 cc.

The order of mixing, which remained unchanged from 1860 to 1900, required that the citric acid be dissolved in the water, the magnesia or magnesium carbonate added, and the mixture stirred until solution was effected. The solution was then filtered into a 12 fluid ounce bottle containing the syrup of citric acid. The potassium bicarbonate was added, the bottle stoppered securely, and shaken occasionally until solution was effected.

In the U. S. P. IX 60 cc. of syrup were substituted for the syrup of citric acid and 5 grams of purified talc and 0.1 cc. of oil of lemon were added to the formula. The order of mixing remained the same except that hot distilled water was used and the mixture of citric acid, magnesium carbonate, and syrup was heated to its boiling point before the oil of lemon, previously triturated with purified talc, was added. This mixture was then filtered into a 12 fluid ounce bottle, the potas-

sium bicarbonate added, and the bottle stoppered. The only change in the U. S. P. X formula was the increase of the citric acid from 33 to 35 grams. In the U. S. P. XI this quantity of citric acid was reduced to 33 grams.

A considerable amount of work has been done on this preparation, and probably the most significant is that performed by Stevens (5) in 1890. He advocated the use of citric acid and magnesium carbonate in such proportions that the finished Solution of Magnesium Citrate would contain the acid citrate ($MgHC_6H_5O_7 = 213$). The equation which he offered is given below.

$$\underset{484}{(MgCO_3)_4Mg(OH)_2.5H_2O} + \underset{1050}{5H_3C_6H_5O_7.H_2O} \rightarrow \underset{1070}{5MgHC_6H_5O_7} + \underset{176}{4CO_2} + \underset{288}{16H_2O}$$

He states that this acid salt is always present when citric acid is in excess of the above proportions while predominance of magnesium or the magnesium ion will produce a neutral tribasic salt ($Mg_3(C_6H_5O_7)_2$) having a molecular weight of 450 in the anhydrous form. In the crystalline form the compound contains ten molecules of water of hydration and has a molecular weight of 630. He also claims that the acid salt is therapeutically the more active. Stevens suggested the following proportions for the formula.

Magnesium Carbonate	121 gr.	7.84 Gm.
Acid for the reaction	262.5 gr.	17.05 Gm.
Acid for Potassium salt	21 gr.	1.36 Gm.
Citric Acid in total	283.5 gr.	18.41 Gm.
Potassium Bicarbonate	30 gr.	1.94 Gm.

It is interesting to note that this formula corresponds very closely to the amounts which would be necessary if four-sevenths of the amounts of the U. S. P. XI formula were used as suggested by Scoville (3). This would equal 8.57 grams of magnesium carbonate and 18.85 grams of citric acid.

In 1926 England (6) stated that the U. S. P. IX solution was too acid to be palatable and that the U. S. P. X solution was even more so. He claimed that the initial mistake was made in 1890 when

the magnesium carbonate was increased from 13 to 15 grams with an increase in the acid to 30 grams. He believed that the solution to the problem was to return to the official formula of 1870, requiring 12.5 grams of carbonate and 25 grams of acid. In 1929 Neimeth (7) proposed a formula in which only 31 grams of citric acid were used and the finished product contained magnesium salts corresponding to 1.5 grams per 100 cc. of magnesium oxide. This formula, he claimed, would obviate the sour taste of the product and would give a more stable preparation. Kleinschmidt (8) found that 20 per cent less citric acid than the U. S. P. X formula required could be used without precipitation if the solution were subjected to a temperature of 150° F. (65.6° C.) for twenty minutes. It is claimed that during the warming of the solution a portion of the cane sugar is converted to invert sugar and this chemical process is what prevents the formation and precipitation of the less soluble basic magnesium citrate. Through the affinity for water of the invert sugar ($C_{12}H_{22}O_{11} + H_2O \rightarrow 2C_6H_{12}O_6$), the formation of magnesium citrate ($Mg_3(C_6H_5O_7)_2.14$ or $13H_2O$) is inhibited. The amount of water which would be taken up by the 35 grams of sugar suggested in his formula would be 1.84 grams. This is such a small amount when compared to 330 cc. of finished solution that his claims appear rather improbable. The formula which he recommended to the Revision Committee is as follows:

Magnesium Carbonate 40%	14 Gm.
Citric Acid	28 Gm.
Sugar	35 Gm.
Sodium Bicarbonate q. s.	
Flavor q. s.	
To make not more than	330 cc.

The solution is mixed according to the U. S. P. procedure except that the solution is kept at a temperature of 140-160° F. for twenty minutes, filtered hot and immediately bottled, carbonated, and sealed.

In 1932 Oakley and Krantz (9) stated that when a chemical equivalent of magnesium oxide is added to an equivalent of citric acid there exists $MgHC_6H_5O_7$ in equilibrium with a small amount of $Mg_3(C_6H_5O_7)_2$. They thought that a considerable amount of the acid was converted to the neutral salt, which is probably responsible

for the precipitation in the citrate solution. The presence of citric acid would therefore tend to shift the equilibrium to the acid salt and favor stability. Osol and Tice (10) found that with 33 grams of citric acid and 15 grams of the generally marketed magnesium carbonate, a very unsatisfactory product results if the potassium bicarbonate is included according to the directions of the U. S. P. X. They also found that with 33 grams of citric acid per 350 cc. a magnesium carbonate which corresponds to 39.2 per cent of magnesium oxide or its equivalent must be used to give even fairly satisfactory results. If the potassium bicarbonate were not included the product was stable, if sterile, regardless of the quality of magnesium carbonate used. They thought the sterilization in some way retarded precipitation. They found that in many commercial samples at least part of the bicarbonate had been omitted, so they recommended that the U. S. P. permit a greater tolerance in the requirement for citric acid so that the official product would not be subject to precipitation.

Some of the more recent suggestions, such as using saccharin and reducing the present U. S. P. XI formula to four-sevenths of the present requirements, were previously mentioned. A series of modifications of the formula which are outlined in the description of the experimental work was prepared and subjected to study.

Experimental

Assay of Magnesium Carbonate: The magnesium carbonate (Merck and Co., Inc.) was assayed by the U. S. P. XI method to determine the yield of magnesium oxide. The yield of calcium oxide was found to be negligible while the average percentage of magnesium oxide was calculated as 42.19 per cent, which is above the U. S. P. XI requirements of not less than 39.2 per cent and not more than 41.5 per cent. However, it did come within the new U. S. P. XII requirements of not less than 40.0 per cent and not more than 43.5 per cent of magnesium oxide.

Variation in Citric Acid Content: Assuming that the following reaction takes place,

$$3(MgCO_3)_4Mg(OH)_2.5H_2O + 10H_3C_6H_5O_7.H_2O \rightarrow 5Mg_3(C_6H_5O_7)_2 + 12CO_2 + 43H_2O$$

it may be determined that 15 grams of magnesium carbonate of a strength corresponding to 42 per cent magnesium oxide required 21.88 grams of citric acid. For comparison, if $MgHC_6H_5O_7$ were the resulting salt, then 32.83 grams of citric acid would be required for 15 grams of the same magnesium carbonate.

The amount of citric acid was varied from 22.0 grams to 41.8 grams by increasing the amounts progressively by 2.2 grams, all other ingredients being maintained in the same proportion as that shown in the formula of the U. S. P. XI for Solution of Magnesium Citrate. An aqueous solution of citric acid which had been previously assayed and found to contain 0.724 grams of citric acid per cc. was used in preparing the solutions, and each sample was prepared in duplicate. The quantities of citric acid in each solution are shown below.

No.	Volume of Citric Acid Solution	Grams of Citric Acid
1	30.39 cc.	22.0 Gm.
2	33.42 cc.	24.2 Gm.
3	36.46 cc.	26.4 Gm.
4	39.50 cc.	28.6 Gm.
5	42.54 cc.	30.8 Gm.
6	45.58 cc.	33.0 Gm.
7	48.62 cc.	35.2 Gm.
8	51.66 cc.	37.4 Gm.
9	54.70 cc.	39.6 Gm.
10	57.74 cc.	41.8 Gm.

Four-Sevenths of the Active Ingredients: Another set of duplicate solutions was prepared by reducing the quantities of magnesium carbonate, citric acid, and potassium bicarbonate to four-sevenths of the amounts specified in the U. S. P. XI, in accordance with the suggestion of Scoville except that the amounts of the other ingredients were not reduced. The quantities required were as follows: magnesium carbonate, 8.57 grams, citric acid, 18.85 grams, and potassium bicarbonate, 1.43 grams. This solution was designated as No. 11.

Substitution of Soluble Saccharin for the Syrup: A third group of solutions was prepared substituting aqueous solutions containing variable quantities of soluble saccharin for the syrup. The quantities

of soluble saccharin used in the solutions are listed below. All other ingredients except syrup were the same as that required in the formula of the U. S. P. XI.

No.	Soluble Saccharin
12	0.05 Gm.
13	0.10 Gm.
14	0.15 Gm.
15	0.20 Gm.

All the solutions prepared by the above procedures were sterilized in an autoclave at 114° C. under 10 pounds of pressure for one-half hour.

Observations: The completed solutions were all clear and had a slight yellow color. They were allowed to stand at room temperature for six weeks and no apparent formation of a precipitate or mold was noticed. Since commercial samples of this solution are usually stored at low temperatures, the solutions were then placed for a period of seven months into an ice box having an average temperature of 10° C. During the seven-month period, all the solutions remained clear except those containing soluble saccharin and Nos. 1 and 2. Solution No. 12, which contained 0.05 gram of soluble saccharin, showed a slight precipitate within four days after being placed into the ice box. Within three weeks every solution containing soluble saccharin showed at least a minute trace of precipitation. However, this amount of precipitation did not increase even after standing seven months. Exactly twenty days after the solutions were placed into the ice box a definite precipitate was observed simultaneously in both samples of No. 1. The precipitation continued gradually until a layer almost an inch thick was formed within a few days. Four days after the first indication of a precipitate in sample No. 1, a similar precipitate appeared in No. 2, which increased until a thick layer was formed on the bottom of the bottle.

At the end of the seven-month period, the solutions were removed from the ice box and compared for flavor. Out of the first ten solutions (1-10) Nos. 5, 6, and 7 had the best flavor and very little difference could be distinguished among them. The solutions having less citric acid were somewhat lacking in flavor while Nos. 9

and 10 were slightly too acid in taste and No. 8 seemed to be somewhere between 6 and 10. Solution No. 11 was somewhat milder than No. 6, but seemed very pleasing and lacked some of the acid taste. Solutions Nos. 12-15 were all very much like No. 6 except No. 15, which was a little too sweet. It was thought that No. 13 or 14 had the most acceptable flavor of the four solutions containing soluble saccharin.

Separation of the Precipitate Formed in Nos. 1 and 2: The precipitate formed in solution Nos. 1 and 2 was separated by filtration and then washed with several portions of water in order to remove any sugar, potassium citrate, or other soluble matter which might have been present. The precipitate was then dried to constant weight in a desiccator, and the percentage of ash (magnesium oxide) determined by igniting weighed samples in a muffle at red heat. The results were 18.13 per cent and 18.17 per cent of magnesium oxide on duplicate samples. These results correspond very closely to the yield of magnesium oxide from magnesium citrate ($Mg_3(C_6H_5O_7)_2.14H_2O$) which yields 17.19 per cent magnesium oxide. Kleinschmidt (7) listed this salt as containing either 14 or 13 molecules of water of crystallization; and should the latter be the case then the magnesium oxide content would be 17.65 per cent, which is even closer to the results obtained above. An old commercial sample of Solution of Magnesium Citrate which was obtained from the Student Health Infirmary also contained a precipitate. This precipitate, when ignited, gave a magnesium oxide content corresponding to 18.00 per cent.

Rees (11) also found the precipitate formed in Solution of Magnesium Citrate to be magnesium citrate ($Mg_3(C_6H_5O_7)_2.14H_2O$). However, he was convinced by experimental evidence that this was the only salt formed by the reaction, while others have inferred that the acid salt ($MgHC_6H_5O_7$) was the chief salt formed. Rees found that solutions prepared by the U. S. P. X formula remained clear for only three months. This did not coincide with the results obtained by us, since solutions containing the amount of ingredients required by the U. S. P. X formula remained clear for at least a year even at low temperatures. He stated that the precipitate could be redissolved into the solution by subjecting the preparation to a temperature of 50° C. for a short period of time, but we could not confirm this statement. Solution No. 1, which contained a large amount of precipitate,

showed no apparent decrease in the amount of precipitate when subjected to a temperature of 50° C. for a period of several days. The precipitate itself had a crystalline appearance and possessed very little taste. Only about 1 part of the salt dissolved in 100 parts of water at 25° C., and the salt dissolved very slowly in dilute acids.

Conclusions

The results obtained by the experimental work just discussed indicate that several general conclusions may be drawn. First of all it is evident that the citric acid does play an important part in the stability of the finished product. However, the increase and decrease of 2 grams of citric acid, which has been made in the last two revisions of the Pharmacopœia, probably had very little effect upon the stability of the finished product, because we obtained stable products even when 20 per cent less citric acid than was required by the U. S. P. XI was used. This coincides with the statement previously made by Kleinschmidt. It was not until the content of citric acid was reduced to 24.2 grams (with 15 grams of U. S. P. XI magnesium carbonate) that precipitation took place. Therefore, it is evident that the citric acid could be reduced even lower than that required by the U. S. P. XI formula if desired. However, there seems to be no definite reason for doing so unless it be to reduce the acid taste which seems to be disagreeable to some, but it is believed that opinions as to taste will vary with individuals. We found very little, if any, difference in the flavor among solutions Nos. 5, 6, and 7 which contained 30.8 grams, 33.00 grams, and 35.2 grams respectively, of citric acid. Since the theoretical amount necessary to form the acid citrate ($MgHC_6H_5O_7$) is slightly over 32 grams and this salt is the most desirable therapeutically as previously stated by Stevens (5), it is believed that at least 33 grams of citric acid should be used for 15 grams of magnesium carbonate. This is the quantity required by the U. S. P. XI formula.

Our results also seem to confirm the conclusions obtained by others who claimed that the salt which precipitates out, if citric acid does not predominate, is magnesium citrate ($Mg_3(C_6H_5O_7)_2 \cdot 14H_2O$).

Should the U. S. P. Revision Committee obtain evidence that the 350 cc. quantity now being dispensed is too large for one dose, then we believe the recommendation made by Scoville of reducing

the quantity of ingredients to four-sevenths of the U. S. P. XI formula, retaining the present volume of the preparation, should be seriously considered. In the preceding experimental work only the quantity of magnesium carbonate, citric acid, and potassium bicarbonate was reduced to four-sevenths of the present requirements. The preparation obtained by this method is very palatable and it would probably be favored by those who dislike the acid taste of the U. S. P. XI product.

The use of soluble saccharin is feasible, but for some reason or other there is a slight precipitation. Even though this precipitate was not pronounced it was nevertheless present and the formation of it should be prevented if possible. The flavor of the preparation was very pleasing and it might be well to consider substituting soluble saccharin for the sugar, not only for use by diabetic patients, but for general use in the present emergency in view of the sugar shortage. The quantity of soluble saccharin which gives the most agreeable flavor was found to be from 0.10 gram to 0.15 gram. Shortly after this work was completed, a similar report upon the use of saccharin was submitted by Zopf (11). He found that 0.15 gram of saccharin was sufficient for a palatable preparation, and that amounts in excess of this gave the bitter taste of saccharin. However, he made no mention of a precipitate being formed.

Summary

A number of magnesium citrate solutions were prepared and sterilized. (a) In the first ten solutions the amount of citric acid was varied by 2.2 grams from 22.0 grams to 41.8 grams, the former figure being the theoretical amount in whole numbers of citric acid required to obtain the normal salt ($Mg_3(C_6H_5O_7)_2$). (b) Solution No. 11 contained four-sevenths of the active ingredients required by the U. S. P. XI. (c) In solutions Nos. 12-15 inclusive, variable amounts of soluble saccharin were substituted for the sucrose. No apparent change was noted in the solutions over a six-week period at room temperature. When placed in an ice box (10° C.), all the solutions containing soluble saccharin showed a minute amount of precipitation within three weeks. The two solutions containing 22.0 grams and 24.2 grams of citric acid respectively showed excessive precipitation within twenty days. The remaining solutions showed no change over a seven-month period in the ice box. Ash determinations

indicated that the precipitate in the solutions containing the smallest proportion of citric acid might be the normal magnesium citrate $Mg_3(C_6H_5O_7)_2 \cdot 14H_2O$). The solution containing four-sevenths of the U. S. P. XI quantities of magnesium carbonate, citric acid, and potassium bicarbonate seemed to be the most palatable, but the ones having 2 grams more or less citric acid than the U. S. P. XI formula were also considered almost equally pleasing in flavor. Solutions containing 0.10 gram to 0.15 gram of soluble saccharin were found to be the most palatable of the saccharin containing solutions.

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SYRUP OF WILD CHERRY

By P. Robert Rasanen and Joseph B. Burt

MANY pharmacists have obtained unsightly preparations when using the U. S. P. XI Syrup of Wild Cherry in combination with alkaloidal salts as a cough preparation. Because of this and many other incompatibilities of Syrup of Wild Cherry, various methods of making the syrup have been proposed. One of the more successful ones is that proposed by Reed, Burrin, and Bibbins (1). The chief object of this method was the extraction of the active ingredients without taking too much of the tannins, which obviously would precepitate the alkaloids.

History

Procter and Turnpenny (2) suggested saturating the Infusion of Wild Cherry with sugar, thereby making a permanent syrup. This Infusion of Wild Cherry was made, contrary to the usual method of making infusions, by cold percolation in order to avoid decomposition of the enzyme and glucoside present. This formula was the one adopted in the U. S. P. of 1850 as the Syrup of Wild Cherry. The formula required five troy ounces of bark with water as a menstruum. The percolate was mixed with the sugar. The formula remained the same until the U. S. P. of 1880 when glycerin was included in the formula, this ingredient being added last. In the U. S. P. of 1890 the Wild Cherry content was increased to 150 grams, the glycerin was mixed with the water and this mixture used as a menstruum. In the U. S. P. VIII the formula was changed again by putting the glycerin in the receiver and allowing the percolated liquid to drop into it. In the U. S. P. IX and X, the formula was changed again to require mixing the glycerin and water, and then using this mixture as the menstruum. In all of the above formulas, the Wild Cherry bark was macerated for twenty-four hours. Scoville (3) suggested that this time be shortened to one hour, since a short maceration with rapid extraction took out less tannin from the drug. Bibbins (4) suggested the addition of 2 per cent alcohol to prevent mold growth. Both of these suggestions were included in the U. S. P. XI formula.

In the method proposed by Reed, Burrin, and Bibbins the glycerin was added to the percolate. Their method is as follows:

Wild Cherry Bark	150 Gms.
Glycerin	150 cc.
Sugar, granulated	675 Gms.
Alcohol	20 cc.
Filtered Percolate, a sufficient quantity,	
To make	1000 cc.

Macerate the bark with a sufficient quantity of distilled water for one hour. Collect 400 cc. of percolate, using additional water as menstruum as needed (filter this percolate brilliantly clear). Add the sugar and dissolve by agitation. Then add the glycerin, alcohol and sufficient filtered percolate to make 1000 cc. and strain.

O'Connell (5) recommended that a moderately coarse powder be used in preparing the official syrup because if extra fine powder is used more tannins are extracted.

Experimental

This syrup was made in the laboratory according to the above formula, using Wild Cherry bark furnished by Dr. H. A. Langenhan. A portion was also made by the U. S. P. formula. In preparing by the U. S. P. method the first cc. portion of the percolate was slightly cloudy, so it was filtered clear through a filter paper. Both syrups were clear but the one made by the proposed method was slightly lighter in color than the U. S. P. syrup. Both syrups had very similar tastes, which were slightly astringent and the odors were about the same.

The following prescriptions (as proposed by Reed, Burrin, and Bibbins) were then compounded, using both syrups and then comparing results immediately and upon standing.

℞ No. 1

Codeine Sulfate		grs. ij
Syrup Wild Cherry	*q. s. ad*	f℥ j

℞ No. 2

Codeine Sulfate		gr. j
Syrup Wild Cherry	*q. s. ad*	f℥ j

℞ No. 3

Codeine Phosphate		gr.	j
Ammonium Chloride		grs.	xv
Syrup Wild Cherry	*q. s. ad*	f℥	j

℞ No. 4

Morphine Sulfate		grs.	ij
Syrup Wild Cherry	*q. s. ad*	f℥	j

℞ No. 5

Codeine Sulfate		grs.	ij
Ammonium Chloride		grs.	xxv
Potassium Iodide		grs.	xxv
Syrup Wild Cherry	*q. s. ad*	f℥	j

℞ No. 6

Codeine Sulfate		gr.	j
Diluted Hydrocyanic Acid		*m*	viiss
Spts. Chloroform		*m*	xiss
Syrup Wild Cherry	*q. s. ad*	f℥	j

℞ No. 7

Codeine Phosphate		gr.	j
Syrup of Tolu		f℥	iv
Syrup Wild Cherry	*q. s. ad*	f℥	j

℞ No. 8

Codeine Sulfate		gr.	j
Ammonium Chloride		grs.	x
Syrup Wild Cherry		f℥	ij
Simple Syrup	*q. s. ad*	f℥	j

Note: The syrup first prepared by the U. S. P. XI method was cloudy so this could not be used for comparison with the proposed syrup as to turbidity produced in prescriptions containing alkaloidal salts. This cloudiness was remedied the second time it was prepared by filtering the first 50 cc. immediately upon obtaining it from the percolator. It was found that if it is not filtered immediately it is almost impossible to remove, by ordinary filtration, the fine precipitate which forms.

Observations: Immediately after preparation all the prescriptions made with the proposed syrup were clear and no haziness or precipitate of any kind was present. They were somewhat lighter than those containing the U. S. P. syrup. The appearances of the prescriptions containing the U. S. P. XI syrup are described below.

Prescription No. 1: slight haziness
No. 2: a barely perceptible haziness
No. 3: a very slight haziness
No. 4: a very slight haziness
No. 5: a definite precipitate
No. 6: a very slight haziness
No. 7: a very slight haziness
No. 8: clear

The prescriptions were again observed after standing six days, using the original syrup for comparison. Those from the proposed syrup were still clear. Those from the U. S. P. syrup showed the following characteristics:

Prescription No. 1: definite haziness
No. 2: slight haziness
No. 3: almost clear
No. 4: very slight haziness
No. 5: precipitate which had settled to the bottom
No. 6: slight haziness
No. 7: definite haziness
No. 8: slight haziness

Conclusions

It is difficult to determine whether the cloudiness which developed upon standing was due to the formation of precipitates or to the growth of molds, but since some of the prescriptions remained clear after standing for three months, it would appear that the former was the case.

Our results were not quite the same as those of Reed, Burrin and Bibbins using the U. S. P. XI syrup, but they were the same in the case of the proposed formula. However, they did not state the length of time they allowed their prescriptions to age. As was shown by us, some of the prescriptions using the proposed syrup did form precipitates within a period of about four weeks.

With the U. S. P. syrup, they found No. 1 gave heavy precipitation, and we found only a slight haziness.* We found No. 5 gave a definite precipitate and they found only a slight haziness. They found No. 7 produced a heavy precipitation, and our sample showed definite haziness and no heavy precipitate until after standing. Otherwise the results were somewhat the same, except that they reported that the U. S. P. syrup showed haziness on standing and ours was still clear after aging three months. The proposed syrup was also clear after three months.

As for stability on aging, we can not say that the proposed formula has a definite advantage. Our U. S. P. syrup may have been more stable because the first 50 cc. of the percolate were filtered, and this is not required by the U. S. P. XI. This was done in order to be sure to obtain a clear syrup so that accurate comparisons of the prescriptions could be made.

The proposed formula gives a syrup somewhat lighter in color than that obtained with the U. S. P. formula, which is probably due to the fact that the glycerin and water mixture extracts more ingredients than the water alone. O'Connell and co-workers (5) state that glycerin should definitely be part of the menstruum in preparing this syrup as in the U. S. P. XI procedure. They felt that the formula of Reed, Burrin, and Bibbins offered little advantage over the U. S. P. XI syrup. However, as far as we can determine, they prepared the syrup by various methods but did not try them in the prescriptions outlined by Reed, Burrin, and Bibbins. Their only reason for insisting that glycerin be used in the menstruum was that it gave a darker syrup. Our comparison of the color of the proposed syrup with that of the U. S. P. XI did show a slight difference in color, but we do not believe this was of sufficient importance to justify the use of glycerin. We found that without the use of glycerin the pharmacist obtains a syrup which will give clear preparations when compounded with alkaloidal salts. Since this syrup is commonly used in this way, we believe the formula of Reed, Burrin, and Bibbins to be a definite improvement over the U. S. P. XI formula.

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*When the U. S. P. syrup which was not filtered was used, definite precipitation was found in No. 1 immediately.

Summary

A method for preparing Syrup of Wild Cherry proposed by Reed, Burrin, and Bibbins was studied. It consisted of adding glycerin to the percolate instead of using it in the menstruum. Numerous prescriptions were compounded which required alkaloidal salts to be dissolved in this syrup. In every instance there was an absence of precipitates of alkaloidal tannates which was not true when the U. S. P. XI syrup was used. The proposed syrup was similar in flavor to the U. S. P. XI syrup and slighter lighter in color.

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WHO DISCOVERED WHAT AND WHO WAS FIRST?

By T. Swann Harding

ON December 20, 1928, the Institution of Electrical Engineers of Great Britain commemorated the invention of the electric incandescent lamp fifty years previously—not by Edison—but by Sir Joseph Swan. While most Americans think that Edison invented the so-called "squirted" filament which stimulated the general use of electric lamps, this vital improvement in the manufacture of carbon filaments was discovered by Swan in 1883. Five years later he had his lamp complete.

Who invented or discovered a thing depends upon what country you inhabit. To an Englishman or American Joseph Priestley discovered oxygen, but a Frenchman attributes the discovery to the great chemist, Antoine Laurent Lavoisier. As Simon Flexner once remarked, a kind of compulsion gets into science and determines its direction. Therefore discoveries are often made almost or quite simultaneously by several investigators. For, to complete the record, Karl Wilhelm Scheele, a German resident in Sweden, also discovered oxygen as far as Germans are concerned.

Some discoveries, of course, occur out of time. They therefore lapse and have to await re-discovery. Science must attain a certain point of development, or new and necessary equipment must be devised, before they can be recognized fully and put efficiently to use.

Thus, in 1880, Pierre and Paul Curie found that sensitive crystals of certain types like Rochelle salt and quartz shrank and swelled under electric shocks. This meant that electrical energy was changed into mechanical energy and it was a very important discovery indeed. Furthermore, when the crystals were squeezed or stretched they generated electrical charges. But there the matter ended for thirty-seven years.

In 1917 a wartime physicist was looking around for some method of detecting sound waves emitted by submerged submarines. He hit upon this observation of the Curies. By further investigation he developed piezo-electric crystals. The long delay must be attributed largely to lack of good methods for subjecting the crystals to rapid electric shocks.

In other words electronic vacuum tubes had to be invented before this discovery could be put to work. The finding is now used in radio broadcasting stations, telephones, phonographs, in cracking

crude oil, precipitating smoke, detecting icebergs and other objects at sea, speeding up cucumber pickling, detecting the stresses in a moving locomotive, and for producing the most accurate clocks in the world.

Most scientific discoveries are made gradually and involve many people. Laymen customarily hear of the last fellow who put the thing across. That is unfortunate for those who went before. It is a fact that insulin, for instance, was not only discovered but utilized in animal experiments long before the Canadian investigators who made all the money and got all the medals did the same thing over again, but they put it across.

It was the same with smallpox vaccine over two centuries ago. For in 1713, Timoni, a Greek in Constantinople, wrote to a Dr. Woodward in London describing smallpox inoculation. In 1721 such inoculations were tried on children in London. Over two hundred vaccinations were made in 1722 and 1723, but a few fatalities discouraged the operatives and the discovery lapsed.

As early as 1738, however, it was being used at Charleston, S. C., and in 1743 Kilpatrick carried out a number of inoculations in London again. Others attenuated the sera, a very modern step. Jenner, to whom we usually attribute the discovery, only managed to get born in 1749. In 1775 it was suggested by Lettsom that infants could be vaccinated in their homes. So the discovery was well in use by 1798 when Jenner first published on the subject.

Many years later, although Drs. Whipple, Minot, and Murphy were awarded the Nobel Prize for their discovery of the value of liver therapy in anemia, others had gone before. Prof. Alfonso Pirera of Naples had, under the direction of Prof. Pietro Francesco Castellino, carried on carefully controlled experiments on dogs and rabbits in 1910-12, using liver therapy successfully. Later they proved the clinical value of liver, liver juice, and liver extract in treating anemia.

As one writer expressed the matter: "To Whipple, Minot, and Murphy goes the credit for establishing, on a scientific basis, the general use of liver in the treatment of anemia. Priority for the early observation and the discovery (experimentally and clinically) of the value of liver and liver injections in the treatment of anemia should, in all fairness, go to the late Professor Castellino and his associate, Professor Alfonso Pirera."

Similarly Darwin put evolution over, though many others had outlined the theory before him, and Schwann gained acceptance for

the cell theory. For Robert Hooke, in his *Micrographia,* published in 1665, described cork and various other plant tissues as composed of pores or cells, and that was nearly two centuries before Schwann published on the subject.

Leeuwenhoek, in 1674, also noted the cellular structure of the leaves of plants and trees, and Wolff, in 1759, called these formations cells. Many other observations were published along this line until Robert Brown in 1833 described even the cell nucleus. Schwann merely rounded out the conception and gained acceptance for it.

In much the same way Erwin F. Smith, the Department of Agriculture's famous specialist on plant diseases, did not, as is often thought, himself show that bacteria could cause plant ills. That discovery was made by T. J. Burrill of Illinois. Smith, however, rounded out the concept and, in a series of brilliant polemical set-tos with, in the main, German opponents, he gained acceptance for what was then regarded as a revolutionary idea. For it seemed just too absurd that germs could cause plant diseases, yet they did—and still do.

Certainly the person who has the organizing ability to round out a scientific principle and the drive to put it over deserves a great deal of credit. Otherwise the discovery could remain locked up in some obscure journal for half a century, as did that of Gregor Johann Mendel on the principles underlying heredity. However, it must also be remembered that the progress of science up to a certain point is often necessary to give the propulsive drive to a discovery.

In late 1931 the structural formula of rotenone and related compounds, insecticides which became extremely valuable, was established by LaForge and Haller, Department of Agriculture chemists. Their paper was received by the *Journal of the American Chemical Society* on November 30, 1931: it was published February 5, 1932. Structural formulas are diagrammatic architectural monstrosities that have to be determined before any chemical compound can be properly understood.

Meanwhile, however, a German investigator had begun an investigation on rotenone in 1926. In an article submitted to *Liebig's Annalen* on February 10, 1932, and published the following March 4, he submitted a formula identical with that of LaForge and Haller! The German investigator received a copy of the LaForge and Haller article as he was correcting the proofs of his own.

That did not end the matter, though. For an Englishman, Robertson, submitted to the *Journal of the Chemical Society* of London, on February 27, 1932, an article giving the same identical for-

mula LaForge and Haller had worked out. He was even able to show that he had communicated his views privately to an Oxford professor before he saw the Americans' paper. Robertson's article was published May, 1932.

But in the *Berichte* of the German Chemical Society for June 8, 1932, there was also a paper by certain Japanese investigators who gave a structural formula for rotenone identical with that proposed by the Department of Agriculture investigators who gained so narrow a priority. Here was the same discovery announced by four different groups of investigators in four different countries, almost simultaneously, a happening probably without parallel in the history of chemistry.

Finally, a discovery that appears to be of only academic interest often finds extensive practical use when others get hold of it. A case in point is Dr. Irving Langmuir's finding that films of oil only a molecule in thickness could be spread on the surface of water. This seems mildly interesting, but not very important. However, Dr. Katherine Blodgett was enabled by this discovery to make invisible glass.

She found that if a piece of glass were dipped in a film of oil floating on water, the oil was transferred to the glass. By her method glass was so coated as to transmit 99 per cent of the light striking it instead of the usual 92 per cent. For this purpose the glass coating must be of just such thickness as to cause the crest of one light wave to overlap the trough of another as the light tries to reflect. This means a coating equivalent to one-fourth of the length of a light wave, or four-millionths of an inch. It took repeated experiments, of course, to get the film of the required thickness.

Once more coincidental discovery dogs our trail here. For twenty-four hours after Blodgett's announcement, Dr. C. Hawley Cartwright described to the American Association for the Advancement of Science, at Richmond, his invisible glass. He had made his product by coating glass with an invisible film of aluminum fluoride four-millionths of an inch thick.

This again goes to prove not only that it often takes several investigators to make and gain acceptance for a scientific discovery, but that several investigators are prone to discover the same thing at just about the same time. As in the case of Robert Fulton's steamboat it is a question of who discovered what—and when, for other nations esteem others than Fulton as the inventor of the steamboat.

SELECTED ABSTRACTS

Penicillin in the Treatment of Infections: a Report of 500 Cases. Statement by the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council. C. S. Keefer *et al. J. A. M. A. 122,* 1217 (1943). Penicillin was found to be most effective in the treatment of staphyloccocic, gonococcic, pneumococcic and hemolytic streptococcus infections. It was found to be particularly effective against gonococcic infections which were resistant to sulfonamide therapy. It was not effective in the treatment of bacterial endocarditis.

The drug was administered intravenously, intramuscularly or topically. For the first two methods a solution of the powder in either isotonic sodium chloride solution or 5 per cent dextrose solution is recommended; for intravenous injection the concentration may be between 1,000 and 5,000 Oxford units per cc., while the latter figure is suitable for the intramuscular technic. If constant intravenous therapy is to be used, the concentration should be 25 to 50 units per cc. For topical application solutions of the drug in isotonic solution of sodium chloride in concentrations of 250 to 500 units per cc. are satisfactory. The powdered sodium salt should not be applied to wound surfaces since it is irritant.

In order to maintain an effective level of penicillin in the blood and tissues it is necessary to inject the drug at intervals of three or four hours, since after intravenous or intramuscular administration it is excreted rapidly in the urine.

Serious staphylococcic infections appear to require a total of 500,000 to 1,000,000 units, treatment being extended over ten days to two weeks. Cases of gonorrhea resistant to sulfonamide therapy have been satisfactorily treated by the injection of 100,000 to 160,000 units over a period of forty-eight hours. Pneumococcic pneumonia patients frequently recovered following the use of 100,000 units given over a period of three days.

Toxic effects arising from administration of penicillin are rare. Despite the fact that the material under test was doubtless crude, representing possibly not more than 10 or 15 per cent pure penicillin,

only a relatively small number of the 500 cases exhibited symptoms of reaction to the drug. Thrombophlebitis at the site of injection, urticaria, chills and fever or fever alone, headache with flushing of the face, and gluteal tenderness at the site of injection were those chiefly noted.

Adjuvant Alkali Therapy in the Prevention of Renal Complications from Sulfadiazine. D. R. Gilligan, S. Garb, C. Wheeler and N. Plummer. *J. A. M. A. 122,* 1160 (1943). Renal complications from sulfadiazine comprise more than half the toxic reactions following the use of this drug and are usually due to a precipitation of some form of it within the kidney or urinary tract. Previous studies of this problem by three of the authors of this paper have been reported; the present paper sets forth additional observations on the effect of alkali therapy upon crystalluria in patients receiving sulfadiazine orally or its sodium derivative intravenously.

Analyses of urinary crystals from patients receiving sulfadiazine orally revealed that they usually consist chiefly of acetylsulfadiazine. Investigation of the solubility of sulfadiazine in buffered solutions and in normal urine emphasized the necessity of administering alkali during the course of treatment, since the compound is twenty times as soluble at pH 7.5 as at pH 5.0. Similarly, acetylsulfadiazine was found to be thirty times as soluble at pH 7.5 as at pH 5.0.

Examinations of the urine of seventy-three patients receiving from 4 to 6 gm. of sulfadiazine daily and varying amounts of sodium bicarbonate were made. Crystals were found in 27 per cent of 172 acid specimens, but were present in only 1.4 per cent of 147 neutral or alkaline specimens. A group of nine patients who received daily from 12 to 15 gm. of sulfadiazine orally and 19.5 gm. of sodium bicarbonate in divided doses over a period of several weeks showed no crystalluria or evidence of renal complications.

A total of sixty-one urine specimens from twenty-three patients who received 5 gm. of sodium sulfadiazine intravenously daily for from two to four days with no adjuvant alkali therapy revealed the incidence of crystalluria to be 43 per cent. Most of the urines were acid. Two other patients who received intravenously 1,000 cc. of sixth normal sodium lactate solution daily in divided doses as an

adjuvant to the sodium sulfadiazine therapy showed no crystalluria; the urine of each was alkaline.

On the basis of clinical studies the authors recommend 15.6 gm. daily of sodium bicarbonate, divided into six doses, as the amount required to maintain the urine neutral or slightly alkaline during sulfadiazine therapy in adults. If preferred, 20.8 gm. of sodium lactate or 18.2 gm. of sodium citrate may be used instead.

Other authors have reported that crystalluria is rarely seen in sulfanilamide therapy, a fact attributable to the greater solubilities of this drug and its acetyl derivative in comparison to sulfapyridine, sulfathiazole and sulfadiazine and their acetylated forms. Clinical experience has demonstrated that adjuvant alkali therapy is of no aid in preventing renal complications from sulfapyridine, since both it and its acetyl derivative show no increase in solubility with increase in pH within the physiologic range of urinary pH.

Clinical studies by several authors on sulfamerizine and sulfamethazine have recently been published. Interest in these sulfadiazine derivatives has been prompted by the fact that both of these compounds, as well as their acetyl derivatives, exhibit greater solubility in the acid range of urinary pH than do sulfadiazine and acetylsulfadiazine.

Prophylactic Use of Sulfathiazole in Oral Surgery: A Clinical Study. H. W. Helbraun. *J. A. D. A. 30,* 1197 (1943). The efficacy of sulfathiazole employed locally as a dusting powder as a prophylactic against infection and in controlling post-operative pain was studied in a group of 100 unselected surgical cases of the mouth. Fifty of the patients received the sulfonamide therapy, which consisted in swabbing the area free of blood and saliva, followed by dusting the sockets and bruised tissues with from 3.8 gr. to 7.7 gr. of powdered sulfathiazole. These patients were permitted no mouth wash or sedative treatment.

The control group of fifty patients used warm saline rinses three to four hours after operation, and 10 gr. of acetylsalicylic acid for sedation.

The 100 cases involved single and multiple extractions of a total of 237 teeth, of which seven were impacted; there were fifteen alveolectomies and the extirpation of four large cysts.

It was observed that for controlling post-operative pain and infection in cases of slight trauma, sulfathiazole therapy locally was not superior to the treatment received by the control group. However, under conditions of excessive trauma local sulfathiazole therapy markedly reduced post-operative pain, and also hastened the healing of tissues. In no case was there dry socket or other infection in any member of the experimental group, though one such case was seen in the control group. In no case was there any untoward reaction to the sulfonamide.

The Comparative Toxicity of Chloral Alcoholate and Chloral Hydrate. W. L. Adams. *J. Pharmacol. and Exper. Therap. 78,* 340 (1943). In an attempt to determine the accuracy of the oft-repeated warning against combining chloral hydrate and alcohol in the same solution the author investigated the hypnotic potencies, acute toxicities, and chronic toxicities of 4 per cent aqueous solutions of crystalline chloral alcoholate (Eastman Kodak Co.) and chloral hydrate administered by stomach tube to the rat. The qualitative responses observed in each phase of the study were indistinguishable, leading to the conclusion that chloral alcoholate is not more toxic than the hydrate.

In hypnotic effects the two drugs exhibited no practical difference. The acute toxicity observations showed that the alcoholate is slightly less toxic than the hydrate in the rat. Additional studies carried out on rabbits, cats and dogs substantiated this conclusion. Chronic toxicity studies did not support the contention that chloral alcoholate is an especially toxic substance.

It was noted that cats are more susceptible to the depressant action of these drugs than any of the other species used in this study.

In the rat the LD_{50} for chloral alcoholate was 0.88 gm. per kg.; for chloral hydrate 0.80 gm. per kg.

Modified Protamine Zinc Insulin: An Improvement on Standard Protamine Zinc Insulin. C. M. MacBryde and H. K. Roberts. *J. A. M. A. 122,* 1225 (1943). A study of 219 well-controlled cases of diabetes over a period of three years revealed that a single daily injection of protamine zinc insulin as a rule established successful regulation only in the mild cases. Moderate or severe diabetes usually required a combined therapy consisting of

separate daily injections of protamine zinc insulin and regular insulin, ordinarily in the proportion of three parts of the former to one of the latter.

In an attempt to simplify this technic the authors employed a modified preparation having 75 per cent slow or precipitated insulin effect to 25 per cent rapid or soluble insulin effect. Such a product is made by the admixture of equal parts of the two insulins at pH 7.2. Comparative studies of the new product made on sixty-two patients showed that in thirty-one of forty-one cases the regulation was as good as or better than that obtained by the use of separate injections of the two insulins. In twenty of the remaining twenty-one milder cases the new modification gave similar results.

Protamine Zinc Insulin Modified for Accelerated Action. A. R. Colwell and J. L. Izzo. *J. A. M. A. 122,* 1231 (1943). The modified protamine zinc insulin used in this study contained two parts of crystalline or regular insulin to one part of protamine zinc insulin, both of the U 80 strength. Its pH was just under 6.0, which is near the isoelectric point of insulin.

Commercial protamine zinc insulin possesses certain faults owing to slow or uncertain release of insulin from its injection depots. These inadequacies consist of a tendency to glycosuria following meals, to hypoglycemia during fasting, especially at night, and unpredictable variations in insulin intensity.

Observations were made on a group of sixty patients, almost all of whom had established diabetes of greater than average severity. The modified preparation corrected the conditions attending the use of the commercial preparation in the majority of the cases studied. The required daily dosage was about 10 per cent less than that used in the ordinary methods because of improved efficiency.

The Absorption Rates of Insulin, Globin Insulin and Protamine Zinc Insulin Labelled With Radioactive Iodine. L. Reiner, E. H. Lang, J. W. Irvine, Jr., W. Peacock and R. D. Evans. *J. Pharmacol. and Exper. Therap. 78,* 352 (1943). In order to study the relative absorption rates of these types of insulin, each was labeled with radioactive iodine by the process of coupling with

p-azoiodobenzene (containing radioactive iodine). The introduction of iodine in this manner causes no significant change in potency, and the insulin azo compound can be obtained in crystalline form if desired. In addition, zinc chloride was added to the globin insulin.

The determinations were carried out on rabbits which received subcutaneous injections of 1.2 I. U. of one of the types of insulin azo compounds. Blood sugar determinations were made prior to the injection and again at a fixed period of time following it. The animals were then sacrificed, and the skin and part of the underlying tissue at the site of the injection excised. The radioactivity counts were made by means of a recording counting rate meter and a Geiger-Müller counter with a filter permitting the measurement of gamma rays only.

The blood sugar curves appeared to justify the assumption that the hypoglycemic activity of the different insulins was not altered by the formation of an azo derivative and the presence of radioactive iodine in the molecule. It also appeared that the radioactive iodine remained coupled to the insulin at least until the latter had exerted its hypoglycemic action, since examination of the excised thyroid glands revealed very little radioactivity.

The time required for protamine zinc insulin to reach the level at which 40 per cent of its radioactivity had disappeared was fifteen times greater than that for insulin; globin insulin was intermediate, requiring three times as long.

Topical Application of Fluoride and Fluoride Absorption. E. J. Largent and J. B. Moses. *J. A. D. A. 30,* 1246 (1943). Numerous studies have confirmed the negative correlation between the incidence of dental caries and the fluoride concentration of drinking water. Since other investigators have advocated the direct application of solutions of sodium fluoride to the teeth as a means of increasing their fluoride content, the authors undertook to determine the extent to which sodium fluoride might be ingested and absorbed through use of this technic.

The study was performed on a human subject in the following manner: (1) the teeth were cleaned; (2) a quadrant was isolated with cotton rolls; (3) a saliva ejector was placed in the mouth; (4) the teeth were dried with warm air; (5) an aqueous solution

containing approximately 0.4 per cent of sodium fluoride was applied; (6) the teeth were again dried with warm air; (7) a second application of the solution was made, followed by drying as before; and (8) the area was irrigated with water, which was carried away by the saliva ejector, the cotton rolls being removed meanwhile. The same procedure was repeated in other areas until all the teeth had been treated.

The entire process required 0.5 ml., equivalent to 2 mg. of fluoride. This represents the maximum quantity available for ingestion from a single treatment, provided that none of the solution was removed by irrigation. Applications were made on five successive days.

The urine and feces of the subject were collected in twenty-four-hour samples for a period of one week before the treatment, and from then on for four more weeks. It was found that the average daily content of fluoride of the urine was 0.666 mg. for the period preceding treatment, 0.554 mg. during the five-day period of treatment, and 0.562 mg. during a twenty-three day period thereafter. The average daily fluoride content of the feces was 0.055 mg.

The authors conclude that there is no appreciable systemic absorption of sodium fluoride following the application of an aqueous solution to the teeth in the manner described.

SOLID EXTRACTS

Diversified Facts of Scientific Interest.

Atabrine is now considered to be as effective as quinine in the treatment of malaria according to a release from the office of the Surgeon General of the Army. The mild toxic symptoms which sometimes develop usually disappear even though the drug is continued. Sodium bicarbonate and sweetened tea given with the drug frequently prevent symptoms. The shortage of the quinine supply has led to the use of Atabrine in all cases of malaria (both suppressive and treatment) except those few in which Atabrine is not tolerated by the patient. Plasmochin is of value only in controlling the spread of the disease since it acts solely on the gametocytes in doses that can be tolerated by the patient.

AJP

The value and virtues of the moldboard plow, used by farmers the world over for more than 200 years, are being disputed by a modern agrarian, Edward H. Faulkner. He states that, while the plow is perfectly satisfactory when being used for its primary purpose of breaking virgin soil, its repeated use on the same ground results in plowing under the organic material that should remain near the surface. There it nourishes crops, but is not available when too far below the roots. A disc harrow is recommended in place of the plow.

AJP

In view of the war-prompted transition from natural rubber to synthetic rubber, we may look forward to seeing most rubber goods used in hospitals and sold as sick-room supplies being black in color. This is due to the presence of carbon black, which is one of the best known materials enhancing the physical characteristics of Buna S synthetic rubber. Therefore, bid farewell, for a time, at least, to the reds and greens and yellows which used to be displayed in such articles.

F. W. Nitardy, well known in pharmaceutical circles, has vouchsafed an interesting theory concerning the relative speed of time, not actually, but in our own minds. For instance, time seems to pass rather slowly to those young people who might happen to give it some thought, while, to an elderly person, time is apparently fleeting with great speed. According to Nitardy, this is due to the fact that to a child of eight, for instance, whose memory covers the four years of his life just passed, one year would represent 25 per cent of this span and, accordingly, be of great moment and of apparent great length. But to a person who has passed the half-century mark, a year represents only 2 per cent or less of his remembered life and its varied happenings, and, thus, appears to be quite short in duration and quick to pass.

AJP

The Medical and Surgical Relief Committee of America, at 420 Lexington Avenue, New York City, has, to date, outfitted more than 600 emergency medical kits to be placed on board coast guard patrol boats, sub chasers, mine sweepers and other vessels of similar nature. These are being used to treat casualties until the ships can reach a base hospital. Drugs, bandages and surgical instruments are included in the donated kits, and the Committee can use more individual contributions of such equipment or money to buy it.

AJP

Victory gardeners, at about this time of year, are beginning to wonder where the corn borers, the bean beetles and other vegetable saboteurs kept themselves in order to attack crops planted in areas which had never before been graced with much more than grass or weeds. Dr. C. H. Curran, of New York, writing in the New York Herald Tribune, says that they have been on the scene of action all the time, and have been hardy enough to feed on the grasses and the weeds until their favorite vegetables came along. It seems that there are no dietary restrictions affecting such pests, just preferences.

BOOK REVIEWS

The Dispensatory of the United States of America, 23rd Edition. By H. C. Wood, Jr. and Arthur Osol, assisted by H. W. Youngken and Louis Gershenfeld. xix + 1881 pp. incl. index. J. B. Lippincott Co., Philadelphia. $15.00.

The United States Dispensatory is so well established as a standard reference in pharmacy and medicine that no discussion is required to prove that it easily ranks as the most important book in pharmacy next to the U. S. P. and the N. F. themselves.

The death of Dr. Charles H. LaWall dissolved that co-authorship so long known of "Wood-LaWall," but Dr. LaWall's place seems to have been well filled by one of his former students and associates, Dr. Arthur Osol, a well-known expert in the field of pharmaceutical chemistry.

The collaborating authors, Dr. Youngken and Dr. Gershenfeld, are likewise men of recognition in the fields of pharmacognosy and bacteriology respectively.

An examination of the text reveals that the general arrangement is along the lines formerly followed. Part I is devoted to the drugs of the U. S. P. XII, the N. F. VII and the B. P. 1932 and its Addenda. Part II considers the unofficial drugs arranged by English title and Part III comprises a very considerable list of processes, reagents, solutions and miscellaneous tables. Insofar as the revision of the subject matter is concerned, the authors have done a remarkably efficient job of bringing the book up to date. It is obviously impossible for a reviewer to examine every detail, but a number of monographs selected at random were found to be complete in every respect and the references cited from recent literature were both very numerous and pertinent. It is evident that a very complete survey of the chemical, pharmaceutical and medical literature has been made.

A number of subjects are presented in such a way that they may be understood by the busy practitioner. Included in this list are articles on glycosides, alkaloids, sterids, amino-acids, surface-active agents, hydrogen-ion concentration, radioactivity, colloids and organic solvents.

The extensive cross index has always been a valuable part of the Dispensatory and that found in this current issue is well done, covering 113 pages.

Tremendous advances in therapy have been made and a host of new drugs have appeared since the previous edition of the Dispensatory. This, together with a new revision of the Pharmacopœia and a new edition of the National Formulary, necessitates a copy of this 23rd edition wherever a modern reference on medicinals is required.

Your reviewer predicts an even greater popularity of this new Dispensatory than that enjoyed in the past. Those familiar with the high standards of previous editions will be agreeably surprised at the even better quality of the current edition.

L. F. Tice.

Synthetic Adhesives. By Paul I. Smith. Chemical Publishing Co., Inc., 234 King Street, Brooklyn, N. Y., 1943. xi + 125 pp. Illustrated. Price: $3.00.

This book describes the uses and properties of various types of adhesives. The types considered are indicated by the chapter headings: I. Dry Glue Film, Phenol-Formaldehyde Resin; II. Phenol-Formaldehyde Liquid and Solid Glues; III. Urea-Formaldehyde Glues; IV. Cellulose Adhesives; V. Polyvinyl Cements; VI. Acrylic Resin Cements; VII. Chlorinated Rubber and Synthetic Rubber Cements; VIII. Miscellaneous Adhesives. These miscellaneous adhesives include the Glyptals, Polystyrene Cements, Metallic Naphthenates and the Arochlors.

In discussing the various types of synthetic adhesives their advantages and disadvantages, time and temperature conditions, solvents employed, commercial sources, characteristics and uses are pointed out. A number of formulas are included. A table is also given which correlates type of resin with application in specified industries and lists the advantages of the resin.

The book is intended as a primer or practical introduction to the field of synthetic adhesives and serves this purpose.

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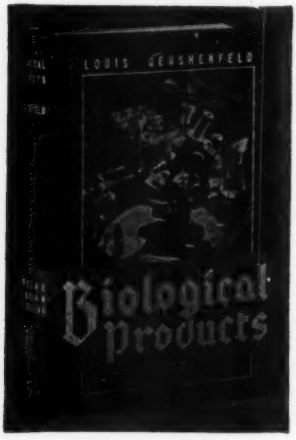

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The paragraph to the left is from "Bacteria and the War", by Dr. Louis Gershenfeld, one of the eight chapters in Popular Science, Volume XIV, entitled SCIENCE IN WAR.

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